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(54) Title: COMPOSITIONS AND METHODS FOR IDENTIFYING A SOLUTION (57) Abstract A composition and method useful to quickly and effectively indicate whether a functional component such as catalase has been added to a clear solution such as a hydrogen peroxide solution involves compounding with the functional component an effective amount of vitamin B-12 such that when the compounded composition is added to the clear solution, the clear solution turns rose colored. By observing the rose color, the user can determine that the functional component has been added to the clear solution.		

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1.

COMPOSITIONS AND METHODS FOR IDENTIFYING A SOLUTIONBackground of the Invention

5 This invention relates to ophthalmically safe compositions for identifying a solution. In particular, the present invention relates to compositions and methods useful to quickly and effectively facilitate the indication of the presence
10 of an eye irritating peroxide in a solution.

Related Art

 Contact lenses are periodically cleaned and disinfected by the user to prevent infection or other
15 deleterious effects on ocular health which may be associated with contact lens wear. Currently there are several different conventional systems and methods which enable the user to clean and disinfect contact lenses between wearing times. In one method the wearer,
20 removes the lenses from the wearer's eyes, and then performs a cleaning regimen using a solution containing a cleansing agent and a saline solution rinse. The lenses are then placed in a disinfecting solution for a suitable period of time, e.g., overnight, such that
25 when the wearer awakens, the lenses have been cleaned and disinfected, ready for placement within the eye, preferably after rising again with saline solution. All of the mentioned solutions are clear thus giving
30 rise to the possibility of confusion among them.

 Conventional cleaning and disinfecting systems can be divided into "hot" and "cold" systems. Hot systems require the use of heat to disinfect the contact lenses; whereas, cold systems use chemical
35 disinfectants at ambient temperatures to disinfect the lenses.

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Within the realm of cold disinfectant systems are hydrogen peroxide disinfection systems. Disinfecting hydrogen peroxide solutions are effective to kill the bacteria and fungi which may contaminate contact lenses. Once the bacteria and fungi are killed, there is sometimes residual, unreacted hydrogen peroxide left in the solution. If the lenses are then removed from the solution, the lenses may have hydrogen peroxide on their surface. Such residual hydrogen peroxide on a disinfecting contact lens may cause irritation, burning or trauma to the eye unless this hydrogen peroxide is neutralized. Therefore, neutralization of the residual hydrogen peroxide in the liquid medium containing the disinfecting contact lens is needed to enable safe and comfortable wear of the disinfecting contact lens.

Aqueous hydrogen peroxide containing solutions currently in use as contact lens disinfectants include relatively high concentrations of hydrogen peroxide, for example, on the order of 3% weight to volume. Such high hydrogen peroxide concentrations are used so that the contact lens can be disinfected in a reasonable period of time, e.g., 10 minutes.

It would be advantageous to provide a contact lens disinfecting system in which it could be readily visually recognized when the residual peroxide is no longer present in the liquid medium containing the disinfecting contact lens.

A typical contact lens cleaning regimen includes a clear saline solution, a clear daily cleaner, a clear disinfecting solution containing 3% hydrogen peroxide, and neutralizing tablets which contain the hydrogen peroxide neutralizer catalase. See U.S. Patent No. 4,585,488 to Gieffer.

In general, the regimen employs the following steps:

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1. Cleaning the lenses with the clear sterile saline solution and the clear daily cleaner solution;
- 5 2. Placing the clean lenses in the clear disinfecting solution and allowing the lenses to soak for a minimum of 10 minutes to overnight; and
- 10 3. Adding to the clear solution the neutralizing tablets to neutralize any residual peroxide; the resulting solution also being clear.

One particular problem associated with this regimen arises from the fact that all of the solutions employed are clear. Thus, the solutions can be easily confused
15 especially if the wearer is tired. If the wearer is not aware that the wearer mistakenly neglects to neutralize the residual peroxide in the disinfecting solution, the wearer could take the lenses from the disinfecting solution and place them directly into the
20 wearer's eye and thereby cause eye irritation. Since the disinfecting solution containing the residual peroxide and the solution containing neutralized peroxide are both clear, it is easy to mix up both solutions. It would therefore be advantageous to
25 provide a contact lens disinfecting regimen whereby the wearer could readily visually differentiate between a solution containing peroxide and one which either contains no peroxide or one wherein the peroxide has been neutralized.

30 U.S. Patent No. 4,863,627 to Davies discloses a contact lens disinfecting composition in solid form for addition to water which includes a contact lens disinfecting agent which is a source of hydrogen peroxide when in water, an inactivating agent to
35 neutralize the hydrogen peroxide source, and a color change indicator such as phenolphthalein which changes from colored in solutions of hydrogen peroxide to

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colorless in essentially neutral solutions. Phenolphthalein, however, is incompatible with contact lenses as it stains the lenses upon soaking.

5 The May 1990 of Spectrum includes an article
entitled "Vitamin and Polymers in the Treatment of
Ocular Surface Disease" which describes an artificial
tear formulation called "Nutra-tear" that contains
approximately 0.05% (w/v) or approximately 500 ppm
10 vitamin B-12. The article discloses that vitamin B-12
attributes a rosy color to the formulation, but the
solution does not stain either clothing or contact
lenses. The vitamin B-12 formulation is topically
applied to the eye to provide relief from dry eye.
15 Vitamin B-12 is also indicated as significantly
reversing or even eliminating epithelial damage that is
a commonly observed factor in ocular surface diseases.

Allergan France also distributes in France an
artificial tear product called "Dulcis" which contains
0.05% vitamin B-12.

20 Various time release tablets having a core
including a hydrogen peroxide destroying component such
as catalase and having a delayed release coating on the
core are known. See for example Schafer et al European
patent Application and Kaspar U.S. Patent No.
25 4,568,517.

Summary of the Invention

The present invention is directed to an
ophthalmically safe composition and method for
30 identifying a solution and more specifically to an
ophthalmically safe composition and method for
indicating the absence of residual peroxide in a
solution resulting from the neutralization of peroxide
in such solution by a peroxidase. The present
35 invention utilizes the ophthalmically safe rose color
inducing vitamin B-12 as an indicator.

5.

Generally, the present invention involves an ophthalmic solution comprising a diluent such as water, an effective amount of vitamin B-12, and further including one selected from the group comprising a peroxide neutralizer, a cleanser, a disinfectant and a salt such as sodium chloride.

Another aspect of the invention involves an ophthalmic tablet comprising an effective amount of vitamin B-12 and a functional component such as, for example, a peroxide neutralizer, cleanser or disinfectant.

In a specific aspect of the present invention, an ophthalmically safe composition for indicating the presence of a peroxide is disclosed. The composition includes a peroxide neutralizing compound and vitamin B-12, preferably in tablet form and optionally coated with a time release coating.

In yet another aspect of the present invention, there is provided an ophthalmically safe method for indicating whether peroxide is present in a solution. The method comprises the steps of formulating a composition containing a peroxide neutralizing compound and an effective amount of vitamin B-12; adding the resulting composition to a solution containing peroxide; and observing the color of the solution.

Detailed Description of the Invention

The present invention is of value where it is important to identify a specific solution and distinguish that solution from others used in an eye care regimen or other regimens where solutions come in contact with a living organism. The present invention is of particular value in facilitating the observation of a solution being free of peroxide.

The present invention takes advantage of the discovery that vitamin B-12 is ophthalmically safe and in solution is rose colored. Such rose color can act

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as an indicia of a solution in which vitamin B-12 is dissolved. By compounding vitamin B-12 with a functional component such as catalase or a disinfectant, one can readily determine whether the functional component has been added to a clear solution.

In one embodiment, the present invention involves use of vitamin B-12 as a safety indicator in lens care regimens which employ hydrogen peroxide. Specifically, in lens care regimens which employ hydrogen peroxide, the lens is typically placed in a solution containing approximately 10 mL of 3% weight to volume hydrogen peroxide. This solution is clear. After the lens is soaked in the hydrogen peroxide solution from 10 minutes to overnight, the lens is disinfected; however, there may be residual hydrogen peroxide left in the solution. The wearer, however, cannot tell whether such residual hydrogen peroxide is left as the solution remains clear. In such care regimen, the user will add to the solution a hydrogen peroxide neutralizing compound such as catalase. Typically the catalase is in aqueous solution or tablet form and optionally may be coated with a time release coating. Vitamin B-12 can be compounded in the tablet such that the tablet will contain the appropriate level of catalase to neutralize residual hydrogen peroxide and an amount of vitamin B-12 effective to change the color of the solution from clear to rose colored.

When the wearer adds the solution or tablet including catalase and vitamin B-12 to the solution containing residual hydrogen peroxide, the solution will become pink or rose colored. Such color will indicate to the user that a hydrogen peroxide neutralizing compound containing tablet has been added to the hydrogen peroxide solution containing the disinfected lens. Any suitable hydrogen peroxide neutralizing component may be included in the present

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compositions. Such hydrogen peroxide neutralizing component should effectively destroy the residual hydrogen peroxide and have no undue detrimental effect on the disinfected lens or on the eye into which the disinfected lens is placed. Among the useful hydrogen peroxide neutralizing components are hydrogen peroxide reducing agents, enzymes useful to destroy hydrogen peroxide, such as peroxidases and catalase, and mixtures thereof.

Examples of the hydrogen peroxide reducing agents which are useful in the present invention are alkali metals, in particular sodium sulfites; thiosulfates; thiourea; thioglycerol; N-acetylcysteine, alkali metal, in particular sodium, formates; ascorbic acid; isoascorbic acid; glyoxylic acid; pyruvic acid; ophthalmically acceptable salts, such as alkali metal and in particular sodium salts, of such acids; mixtures thereof and the like. A particularly useful hydrogen peroxide neutralizing component is catalase since it is often effective to substantially eliminate hydrogen peroxide from a liquid medium in a reasonable period of time, for example, on the order of about 1 minute to about 12 hours, preferably about 5 minutes to about 1 hour, after being initially released in the hydrogen peroxide containing media.

The amount of hydrogen peroxide neutralizing component employed is preferably sufficient to destroy all the hydrogen peroxide present in the hydrogen peroxide containing media into which the hydrogen peroxide neutralizing component is placed. Excess hydrogen peroxide neutralizing component may be employed. Very large excesses of hydrogen peroxide neutralizing component are to be avoided since the hydrogen peroxide neutralizing component itself may cause problems with the disinfected contact lens and/or the ability to safely and comfortably wear such disinfected contact lens. When catalase is employed as

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a hydrogen peroxide neutralizing component, it is preferably present in an amount of about 100 to about 1000, more preferably about 150 to about 700, units of catalase activity per milliliter of liquid medium. For example, an especially useful amount of catalase for use in an aqueous solution containing about 3% (w/v) hydrogen peroxide is about 520 units of catalase activity/ml of solution.

The hydrogen peroxide neutralizing component may be combined with one or more other components, for example, in the core of tablet compounded according to the present invention. Such other components may include, for example, fillers, binders, tonicity agents, contact lens conditioning/wetting agents, buffering agents, lubricating agents and the like. Each of these components may be present, if at all, in an amount effective to perform its designated function or functions. Examples of each of these types of components are conventional and well known in the art. Therefore, a detailed description of such components is not presented here.

An illustrative vitamin B-12 and hydrogen peroxide neutralizing component-containing tablet may have the following composition:

		Wt. %
25	Hydrogen Peroxide Neutralizer	
	Component	1-30
	Vitamin B-12	0.005-1.0
	Filler	15-90
30	Tonicity Agent	1-90
	Buffering Agent	1-50
	Lubricating Agent	0-30

Useful tonicity agents include, but are not limited to, sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof.

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Useful contact lens conditioning/wetting agents include, but are not limited to, polyvinyl alcohol, polyoxamers, polyvinylpyrrolidone, hydroxypropylmethyl cellulose and mixtures thereof. Certain of the present
5 coating components as discussed below may provide one or more other useful functions after being dissolved in the hydrogen peroxide containing media.

Typical saline solutions have a pH in the range of about 6 to 8 and include a buffer component which is
10 present in an amount effective to maintain the pH of the saline solution in the desired range. Among the suitable buffer components or buffering agents which may be employed are those which are conventionally used in contact lens care products. Examples of use for
15 buffer components include those with carbonate functionalities, bicarbonate functionalities, phosphate functionalities, borate functionalities, and the like and mixtures thereof. The buffers may be alkali metal and alkaline earth metal salts in particular sodium and
20 potassium. Acids and bases may be used to adjust the pH of the present compositions as needed.

Useful lubricating agents include, but are not limited to, polyalkylene glycols, such as polyethylene glycols, preferably having molecular weights in the
25 range of about 500 to about 10,000. Other materials conventionally used as lubricants in ophthalmically acceptable tablets may be employed in the tablet of the present invention.

The inclusion of one or more of such other
30 components in the present compositions may be important to facilitate the functioning of such compositions and the present methods. For example, it may be desirable to maintain the pH and/or osmolality of the liquid aqueous medium within certain ranges, for example, to
35 obtain preferred enzyme activities, coating component solubility and/or physiological acceptance. One or more of such other components may be included in the

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mixture which is applied to the core and which remain in the coating. Also, such other component or components may be included in the present compositions separate and apart from the coated core.

5 It should be appreciated that once a catalase tablet is added to a solution having residual hydrogen peroxide, the catalase reacts with the hydrogen peroxide to release oxygen. To the wearer what appears is a bubbling and frothing solution which gets somewhat
10 warm. After the bubbling and frothing has subsided, the neutralization reaction between catalase and hydrogen peroxide is complete. The lenses may thereafter be safely placed within the eyes, although preferably first rinsed with an isotonic saline
15 solution.

 In another embodiment of the present invention, the vitamin B-12 can be added to virtually any ophthalmic solution in an amount which turns the solution pinkish or rose colored. In this manner, a particular solution
20 can be identified and distinguished from other solutions. For example, an effective amount of vitamin B-12 can be added to an isotonic saline solution to thereby turn the solution pinkish color. In this way, the saline solution can be distinguished from other
25 solutions. Vitamin B-12 can also be added to an aqueous peroxide solution, peroxide producing solid dosage forms such as perborates and persulfates, all-in-one cleaning and disinfection solutions and solid dosage forms, and generally to any chemical
30 disinfection solution and/or solid dosage forms including all cleaning and/or disinfection solutions and tablets. Specific commercial examples include the addition of vitamin B-12 to Optifree™ (polyquaternary amine), ReNu™, Oxysept 1™ (hydrogen peroxide), Liquid
35 Enzyme, Oxysept 2 (catalase), and Ultrazyme™ and Heat Enzyme (subtilisin).

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Alternatively, the vitamin B-12 can be added to a disinfecting solution which contains a chemical disinfectant such as Miramine or WSCP. For example, vitamin B-12 can be added to Allergan's® Hydrocare®
5 Cleaning and Disinfecting Solution which contains 0.013% Miramine [tris (2-hydroxy-ethyl) tallow ammonium chloride]; 0.002% thimerosal; bis (2-hydroxy-ethyl) tallow ammonium chloride; sodium bicarbonate; sodium phosphate, dibasic, anhydrous; sodium phosphate,
10 monobasic; propylene glycol; polysorbate, a polyhema; and hydrochloric acid in a sterile isotonic buffered solution. This solution then would become a rose colored solution which could be distinguished from normal isotonic saline solutions which would remain
15 clear. Thus the present invention provides an ophthalmically safe method for identifying a solution by adding an effective amount of vitamin B-12 to the solution to change the color of the solution from clear to rose and observing the color of the resulting
20 solution.

The vitamin B-12 that can be used for the present invention can be either cyanocobalamin or any cobalamin derivatives such as methylcobalamin, hydroxycobalamin, and desoxyadenosylcobalamin provided such derivatives
25 are ophthalmically safe and cause an aqueous solution to change observable color. Preferably cyanocobalamin is used.

The amount of vitamin B-12 used in connection with the embodiments of the present invention is at least
30 that much which when dissolved in an aqueous solution will show an observable color change, and preferably a color change to rose or pink. In general, the amount of vitamin B-12 in solution will preferably range from 5 to 50 parts per million with 8 to 10 parts per
35 million more preferred.

Without limiting the scope of the present invention, examples of hydrogen peroxide neutralizing

12.

tablets formulated according to the present invention are set forth below:

Example 1

5 (No delayed release coating)

	<u>INGREDIENTS</u>	<u>MG/TABLET</u>
	CATALASE CRYSTALLINE BOEHRINGER GRADE 1	1.5
	SODIUM CHLORIDE	89.40
	SODIUM PHOSPHATE DIBASIC ANHYDROUS USP	12.50
10	POLYETHYLENE GLYCOL 3350	1.05
	SODIUM PHOSPHATE MONOBASIC MONOHYDRATE USP	1.00
	CYANO COBALAMINE	0.081

Example 2

15 (With delayed release coating)

	<u>INGREDIENTS</u>	<u>MG/TABLET</u>
	CATALASE CRYSTALLINE BOEHRINGER GRADE 1	1.5
	SODIUM CHLORIDE	89.40
20	SODIUM PHOSPHATE DIBASIC ANHYDROUS USP	12.50
	POLYETHYLENE GLYCOL 3350	1.05
	SODIUM PHOSPHATE MONOBASIC MONOHYDRATE USP	1.00
	CYANO COBALAMINE	0.081
	METHOCEL E15LV PREMIUM (coating)	5.00

25

Example 3(With delayed release coating
and cleaning enzyme)

	<u>INGREDIENTS</u>	<u>MG/TABLET</u>
30	CATALASE CRYSTALLINE BOEHRINGER GRADE 1	1.5
	SODIUM CHLORIDE	89.40
	SODIUM PHOSPHATE DIBASIC ANHYDROUS USP	12.50
	POLYETHYLENE GLYCOL 3350	1.05
	SODIUM PHOSPHATE MONOBASIC MONOHYDRATE USP	1.00
35	CYANO COBALAMINE	0.081
	SUBTILISIN A (in the coating)	0.0031
	METHOCEL E15LV PREMIUM (coating)	5.00

13.

The amount of catalase added was determined by an assay of the batch of product to be used. The above tablets prepared contained about 5200 units of catalase activity.

5 In a typical regimen, one tablet formulated according to the examples can be added to 10 ml of a 3% hydrogen peroxide solution after contact lenses have soaked for at least 10 minutes in the peroxide solution. After the bubbling of the resulting solution has subsided, e.g., about 10 minutes, the solution is pink and the lenses are disinfected yet relatively free of residual peroxide.

10 A time release coated tablet in accordance with Example 2 is used to disinfect a conventional soft contact lens as follows. 10 ml of a 3% (w/v) aqueous solution of hydrogen peroxide is provided at room temperature. The contact lens to be disinfected and the layered tablet are placed in the solution at the same time. For approximately ten (10) minutes, the solution remains substantially quiet, i.e.,

15 substantially no bubbling (gas evolution) takes place and the solution remains clear. For the next approximately 20 to 25 minutes, the solution bubbles. After this period of time, the solution becomes and remains quiet and the color of the solution changes to light rose color. Two hours after the contact lens is first introduced into the solution, it is removed from the solution and placed directly into the wearer's eye. It is found that after one hour, the contact lens is

20 effectively disinfected. Also, the lens wearer experiences no discomfort or eye irritation from wearing the disinfected contact lens. The bubbling of the solution provides an indication that hydrogen peroxide destruction is occurring. An indication that the peroxide destruction is complete is provided when

25 the bubbling stops and the solution is rose colored.

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A coated tablet in accordance with Example 3 is used to disinfect and clean a protein-based debris laden soft contact lens as follows. 10 ml of a 3% (w/v) aqueous solution of hydrogen peroxide is provided at room temperature. The contact lens to be disinfected and cleaned, and the enzyme-containing coated tablet, are placed in the solution at the same time. For approximately ten (10) minutes the solution remains substantially quiet. For the next approximately 20 to 25 minutes, the solution bubbles and becomes pink. After this period of time, the solution becomes and remains quiet. Two hours after the contact lens is first introduced into the solution, it is removed from the solution, rinsed with physiological saline solution to remove the subtilisin A and placed into the wearer's eye. It is found that after one hour, the contact lens is effectively disinfected and cleaned of protein-based debris. The lens wearer experiences no discomfort or eye irritation from wearing the disinfected and cleaned contact lens.

The vitamin B-12 can be added directly to a solution, or may be present in a tablet as illustrated above in the form of, for example, a tablet, capsules, one or more solid particles and the like, which includes a coated portion, for example, a core such as a core tablet containing the vitamin B-12 and for example, a catalase, and a barrier component coating. The barrier component can act to delay the release of the catalase and vitamin B-12 from the core portion for a period of time, preferably sufficient to allow the lens to be disinfected.

The delayed release of the vitamin B-12 and/or catalase into the liquid medium may be accomplished in any one of many suitable ways, a number of which are conventional and well known in the art. For example, the barrier component, for example a coating, may consist of a slowly dissolving coating material.

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Barrier components suitable as either coating or as a matrix include water soluble vinyl polymers such as poly vinyl pyrrolidone, polyvinyl alcohol and polyethyleneglycol; water soluble protein;

5 polysaccharide and cellulose derivatives such as methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose; alginic acid and its salts and other derivatives; and the like and mixtures thereof.

The amount of barrier component used is not

10 critical in the present invention provided that such barrier component functions as described herein. The barrier component or components may be suitably present in the range of about 1% to about 60%, based on the weight of the catalase and vitamin B-12.

15 A preferred delayed release coating or barrier coating is derived from a mixture comprising water, a ketone component and a water soluble coating component. This mixture is applied to the hydrogen peroxide neutralizing component-containing core in an amount

20 sufficient to coat the core, in particular substantially all of the core, and form a precoated core. At least portions of the water and ketone component are removed from the precoated core to form the coated core, i.e., the core with a barrier coating.

25 The water soluble coating components useful in the present invention include those coating components which dissolve in water over a period of time. The coating component or components chosen for use should have no substantial detrimental effect on the lens

30 being treated, on the disinfecting and cleaning of the lens, or on the person in whose eye the disinfected/cleaned lens is to be placed. The coating component or components used in the present barrier coatings and the amount or thickness of the barrier

35 coating are preferably chosen so that the barrier coating dissolves into the hydrogen peroxide containing media after a period of time sufficient for the

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hydrogen peroxide to disinfect the lens located in the hydrogen peroxide containing media.

5 The water soluble coating component or components may be chosen from ophthalmically acceptable materials, preferably polymeric materials, which function as described herein. Particularly useful coating components include water soluble cellulose derivatives, water soluble methacrylate-based polymers, water
10 soluble vinyl pyrrolidone-based polymers and mixtures thereof. Mixed polymers of methyl vinyl ether and maleic acid anhydride, and polyvinyl alcohols can also be used.

The water soluble methacrylate-based polymers include polymers derived from methacrylic acid and/or
15 methacrylic acid esters. Water soluble vinyl pyrrolidone-based polymers useful in the present invention include polymers derived in whole or in part from vinyl pyrrolidone, such as polyvinylpyrrolidone, polyvinylpyrrolidone derivatives, such as ethers and
20 esters, and mixtures thereof. A specific example of useful water soluble vinyl pyrrolidone-based polymers is polyvinylpyrrolidone acetate, such as the product sold by BASF under the trademark Kollidon VA-64. Water soluble methacrylate-based polymers, water soluble
25 vinyl pyrrolidone polymers and mixtures thereof are quite useful.

The more preferred water soluble coating components comprise at least one water soluble cellulose derivative.

30 The water soluble cellulose derivatives useful in the present invention can be obtained by derivatizing cellulose to achieve the desired degree of water solubility. Substituent groups selected from hydrocarbon groups and substituted hydrocarbon groups
35 are particularly useful for inclusion in the present cellulose derivatives. Such substituents which include 1 to about 10 carbon atoms, and such groups which

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include a polar group, such as a hydroxyl group, a carbonyl group, a carboxyl group and the like, are very effective in providing cellulose derivatives with the desired water solubility. Such water soluble cellulose derivatives can be produced using conventional and well known organic synthesis techniques.

The water soluble cellulose derivatives can be selected from water soluble cellulose ethers, water soluble cellulose esters and mixtures thereof, preferably water soluble cellulose ethers and mixtures thereof. Examples of water soluble cellulose esters include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and the like.

Water soluble alkyl ethers and/or hydroxyalkyl ethers of cellulose are among the water soluble cellulose ethers which can be employed. The alkyl groups preferably have 1 to about 6, more preferably 1 to about 3 or 4, carbon atoms. Specific examples of useful water soluble cellulose ethers include hydroxypropylmethylcellulose, ethyl cellulose, methyl cellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, metal, in particular alkali metal, salts of cellulose ethers such as sodium carboxymethylcellulose, and the like and mixtures thereof. A particularly useful water soluble cellulose derivative is hydroxypropylmethyl cellulose.

The ketone component or components useful are chosen to provide effective barrier coatings and to have no substantial adverse effect on the activity of the hydrogen peroxide neutralizing component, in particular catalase, or on the activity of the cleaning enzyme or enzymes, if any, present in the present composition. The ketone component or components have the characteristic ketone structure and are preferably selected from ketones having 3 to about 6 carbon atoms per molecule. The ketone component or components may include one or more substituent groups provided that

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such group or groups do not substantially interfere with the functioning of the ketone component or components in the present invention. Specific examples of useful ketone components include acetone, methyl ethyl ketone, methyl isobutyl ketone and the like and mixtures thereof.

The relative amounts of water, ketone component, and water soluble coating component employed are preferably selected to achieve effective barrier coatings with little or no degradation in the activity of the hydrogen peroxide neutralizing component, and cleaning enzyme or enzymes, if present. More preferably, water is present in the mixture in a minor amount, i.e., less than about 50% (v/v), and the ketone component is present in the mixture in a major amount, i.e., more than about 50% (v/v), of the total amount of water and ketone component present in the mixture. Relatively high concentrations of water have been found to have a detrimental effect on the activity of the hydrogen peroxide neutralizing component, in particular catalase, in the item or items. For this reason, it is still more preferred to include no more than about 20% (v/v) water in the mixture. However sufficient water is preferably present in the mixture to insure that the water soluble coating components is completely solubilized in the mixture. With the coating component completely solubilized in the mixture, the barrier coating has good uniformity, for example, substantially uniform thickness, and has reliable and predictable delayed release characteristics. Coated cores produced from mixtures without water tend to have less uniform barrier coatings and to have less reliable and predictable delayed release characteristics.

The amount of water soluble coating component included in the mixture is such as to form a barrier coating on the core with the desired delayed release characteristics. Preferably, the amount of such

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coating component is such as to be completely solubilized in the mixture. In one embodiment, the amount of coating component present in the mixture is in the range of about 0.1% to about 20%, preferably about 0.2% to about 10% and more preferably about 0.5% to about 5%, (w/v) of the total mixture.

A particularly useful mixture includes 3% (w/v) of hydroxypropylmethyl cellulose in a liquid medium of 90% (v/v) of acetone and 10% (v/v) of water.

The mixture may include one or more other components which act, for example, to facilitate applying the mixture to the core, to facilitate removing water and/or ketone component or components from the precoated core, and/or to provide a barrier coating with one or more useful properties and/or components which are useful to treat the lens when released in the hydrogen peroxide containing media. For example, the mixture may include one or more lubricating agents and/or deposit prevention agents to assist in maintaining the integrity of the barrier coating and to reduce deposit formation in the liquid aqueous medium in which the composition is used

In certain instances, e.g., where the coating component is relatively hygroscopic, a final protective coating, for example, comprising one or more water soluble cellulose derivatives, may be applied to the coated or outer coated item or items, in particular using the method of the present invention, to protect the coated or outer coated item or items, such as during storage. This protective coating, which is often relatively thin, dissolves into the liquid aqueous medium very quickly, preferably substantially immediately, after the protected item or items are first contacted with the liquid aqueous medium.

The mixture, preferably a liquid solution, can be applied to the barrier coated core employing any conventional technique used, for example, to apply a

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liquid precursor of a delayed release coating to an item, such as a tablet, pill, microgranule, powder and the like. For example, the mixture can be sprayed onto the barrier coated core. Alternately, the barrier coated core can be dipped into the mixture. Conventional fluidized bed techniques can also be used.

The barrier coated core is subjected to conditions effective to remove, e.g., evaporate, at least a portion of the water and ketone component from the barrier coated core and form the coated core. Such conditions include, for example, ambient or slightly elevated temperatures.

In another embodiment of the present invention, vitamin B-12 can be added to a composition which is known to be effective to remove certain debris from a contact lens thus generating a rose colored solution when such compositions are employed in a liquid media.

In a particularly useful embodiment, such compositions include at least one enzyme effective to remove debris from a contact lens. Among the types of debris that form on contact lens during normal use are protein-based debris, mucin-based debris, lipid-based debris and carbohydrate-based debris. One or more types of debris may be present on a single contact lens.

The enzyme employed may be selected from peroxide-active enzymes which are conventionally employed in the enzymatic cleaning of contact lenses. For example, many of the enzymes disclosed in Huth et al. U.S. Reissue Patent 32,672 and Karageozian et al. U.S. Patent 3,910,296 are useful in the present invention. These patents are incorporated in their entirety by reference herein. Among the useful enzymes are those selected from proteolytic enzymes, lipases and mixtures thereof.

A preferred group of proteolytic enzymes are the derived alkaline proteases generically called

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subtilisin enzymes. Reference is made to Deayl, L., Moser, P.W. and Wildi, B.S., "Proteases of the Genus *Bacillus*. II Alkaline Proteases", *Biotechnology and Bioengineering*, Vol. XII, pp 213-249 (1970) and Keay, L. and Moser, P.W., "Differentiation of Alkaline Proteases from *Bacillus* Species" *Biochemical and Biophysical Research Comm.*, Vol. 34, No. 5, pp. 600-604 (1969).

The subtilisin enzymes are broken down into two subclasses, subtilisin A and subtilisin B. In the subtilisin A grouping are enzymes derived from such species as *B. subtilis*, *B. licheniformis* and *B. pumilis*. Organisms in this sub-class produce little or no neutral protease or amylase. The subtilisin B sub-class is made up of enzymes from such organisms as *B. subtilis*, *B. subtilis* var. *amylosacchariticus*, *B. amyloliquefaciens* and *B. subtilis* NRRL B3411. These organisms produce neutral proteases and amylases on a level about comparable to their alkaline protease production. One or more enzymes from the subtilisin A sub-class are particularly useful.

In addition other preferred enzymes are, for example, pancreatin, trypsin, collagenase, keratinase, carboxylase, aminopeptidase, elastase, and aspergillopeptidase A and B, pronase E (from *S. griseus*) and dispase (from *Bacillus polymyxa*).

An effective amount of enzyme is to be used in the practice of this aspect of the present invention. Such amount will be that amount which effects removal in a reasonable time (for example overnight) of substantially all of at least one type of debris from a lens due to normal wear. This standard is stated with reference to contact lens wearers with a history of normal pattern of lens debris accretion, not the very small group who may at one time or another have a significantly increased rate of debris accretion such

that cleaning is recommended every day, or every two or three days.

5 The amount of enzyme required to make an effective cleaner will depend on several factors, including the inherent activity of the enzyme, and the extent of its interaction with the hydrogen peroxide present.

10 As a basic yardstick, the working solution should contain sufficient enzyme to provide about 0.001 to about 3 Anson units of activity, preferably about 0.01 to about 1 Anson unit, per single lens treatment. Higher or lower amounts may be used.

15 Enzyme activity is pH dependent so for any given enzyme, there is a particular pH range in which that enzyme will function best. The determination of such range can readily be done by known techniques.

20 In yet another aspect of the present invention, the vitamin B-12 can be added as an identifying color producing component to tablets or solutions containing disinfecting or antimicrobial agents such as quaternary ammonium salts used in ophthalmic applications such as poly[(dimethyliminio)-2-butene-1, 4-diyl chloride, α - [4-tris(2-hydroxyethyl) ammonium-2-butenyl-w-tris(2-hydroxyethyl)ammonium]- dichloride (chemical registry number 75345-27-6) generally available as

25 Polyquaternium 1® from ONYX Corporation and benzalkonium halides, WSCP, WSCP/Croquat, chlorine dioxide, and biguanides such as salts of alexidine, alexidine free base, salts of chlorhexidine, hexamethylene biguanides and their polymers. See U.S.

30 Patent No. 4,758,595 incorporated herein.

The salts of alexidine and chlorhexidine can be either organic or inorganic and are typically disinfecting nitrates, acetates, phosphates, sulphates, halides and the like. Preferred antimicrobial agents

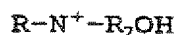
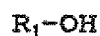
35 include the biguanides with hexamethylene biguanides, their polymers and water-soluble salts being most preferred. Generally, the hexamethylene biguanide

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polymers, also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in U.S. Patent No. 4,758,595 which is incorporated herein by reference.

Another compound which meets the foregoing criteria when detoxified is a compound having structural Formula A. See U.S. Patent No. 4,029,817 assigned to Allergan, Inc. which is incorporated herein by reference.

Formula A



wherein R is an alkyl or alkenyl radical having 12-20 carbon atoms and preferably a tallow radical, i.e., composed of mixtures of $-C_{17}H_{34}$ and $-C_{17}H_{35}$; and R_1 , R_2 , and R_3 are the same or different and represent alkyl radicals having 1 - 3 carbon atoms. This compound should be used together with a detoxifying amount of a non-toxic compound selected from the group consisting of water soluble polyhydroxyethyl methacrylate, carboxymethylcellulose, non-ionic surfactants such as polyoxyethylene sorbitan fatty acid esters and polyoxyethylene ethers, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropylmethylcellulose and mixtures thereof.

The preferred compound of the above Formula A is alkyl triethanol ammonium chloride wherein the alkyl group is a tallow radical. This compound is known as Miramine TA-30® and is commercially available from the Miranol Chemical Company. The preferred compound can be obtained as a 30% aqueous acidic solution. The compound is fairly stable in acidic pH but tends to precipitate out of solution as the base under alkaline conditions.

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The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made without departing from the spirit or scope of the invention.

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WHAT IS CLAIMED IS:

1. An ophthalmically acceptable composition for neutralizing residual peroxide and indicating the absence of such peroxide, the composition comprising:
a peroxide neutralizing compound; and
5 an effective amount of vitamin B-12.
2. The ophthalmically acceptable composition of claim 1 wherein the peroxide neutralizing compound is catalase.
3. The ophthalmically acceptable composition of claim 1 wherein there is present from 0.005 to 1.0 weight percent of vitamin B-12.
4. The ophthalmically acceptable composition according to claim 1 further including a delayed release coating covering the catalase.
5. An ophthalmically safe method for identifying a solution, the method comprising the steps of:
adding an effective amount of vitamin B-12 to the solution to change the color of the solution from clear
5 to rose; and
observing the color of the solution.
6. The method of claim 5 wherein there is present from 5 to 50 ppm of vitamin B-12 added to the solution.
7. An ophthalmically safe composition comprising an effective amount of vitamin B-12 and another component selected from the group consisting of a peroxide producing compound, a peroxide neutralizer, a
5 cleanser, a disinfecting agent, and mixtures thereof.

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8. The composition of claim 7 wherein a peroxide neutralizer is selected and the peroxide neutralizer is catalase.

9. The composition of claim 7 wherein a cleanser is selected and the cleanser is subtilisin A.

10. The composition according to claim 7 wherein a disinfecting agent is selected and the disinfecting agent is Miramine.

11. The composition of claim 7 wherein the other component is hydrogen peroxide.

12. The composition of claim 7 wherein the other component is a quaternary ammonium salt.

13. The composition of claim 7 wherein the other component is sodium chloride.

14. The composition of claim 7 wherein the other component is a biguanide.

15. The composition of claim 7 wherein the other component is chlorine dioxide.

16. The composition of claim 7 wherein the other component is WSCP.

17. The composition of claim 7 wherein the other component is a mixture of WSCP and croquat.

18. The composition of claim 7 wherein the components are present in solid form.

19. The composition of claim 7 wherein the components are present in solution.

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20. The composition of claim 7 wherein the components are present in powder form.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 92/07195

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 L 2/18						
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: bottom; border-right: 1px solid black;">IPC5</td> <td>A 61 L</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in Fields Searched⁸</div>			Classification System	Classification Symbols	IPC5	A 61 L
Classification System	Classification Symbols					
IPC5	A 61 L					
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹						
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³				
X	Contactologia, vol. 100, 1988, Ph. Lapalus et al.: "Wirkung von Vitamin B12 auf die Abheilung von Hornhautwunden beim Kaninchen", pp. 73-75, see especially page 73 col. 1 last part	5-7, 13, 18-20				
A	US, A, 4863627 (D.J.G. DAVIES ET AL.) 5 September 1989, see column 3 lines 9-18	1-20				
A	EP, A1, 0209071 (TITMUS EUROCON KONTAKTLINSEN GMBH) 21 January 1987, see especially claims 36 and 39	1-20				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>						
IV. CERTIFICATION						
Date of the Actual Completion of the International Search 30th November 1992	Date of Mailing of this International Search Report 15 DEC 1992					
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer Kerstin Boije Janson					

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A2, 0426489 (ALLERGAN, INC.) 8 May 1991, see especially claims 5, 14 —	1-20
A	WO, A1, 9112825 (ALLERGAN, INC.) 5 September 1991, see the whole document ---	1-20
A	EP, A2, 0458578 (ALCON LABORATORIES INC) 27 November 1991, see claims 15-19 ---	1-20
A	EP, A1, 0411887 (SCHERING CORPORATION) 6 February 1991, see the whole document ---	1-20
A	US, A, 4568517 (H.H. KASPAR ET AL.) 4 February 1986, see the whole document ---	1-20
A	US, A, 4585488 (G. GIEFER) 29 April 1986, see the whole document ---	1-20
A	US, A, Re 32,672 (S.W. HUTH ET AL.) 24 May 1988, see the whole document -----	1-20

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 92/07195**

SA 64532

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/10/92. The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

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		GB-A-B- 2173017	01/10/86
		JP-T- 62502245	03/09/87
		WO-A- 86/05695	09/10/86
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		EP-A- 0485475	20/05/92
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		JP-A- 60068858	19/04/85
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		EP-A- 0082798	29/06/83
		US-A- 4748992	07/06/88
US-A- Re 32,672	24/05/88	NONE	

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

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